UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/764,649 | 01/26/2004 | Haiyan Xu | MPI03-025P1RNM | 8500 |

30405 7590 05/17/2005

MILLENNIUM PHARMACEUTICALS, INC.
40 Landsdowne Street
CAMBRIDGE, MA 02139

| EXAMINER | |
|---|---|
| HOWARD, ZACHARY C | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1646 | |

DATE MAILED: 05/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/764,649 | XU ET AL. | |
| | Examiner | Art Unit | |
| | Zachary C. Howard | 1646 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *2/22/2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *3-6 and 11-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,7-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1,2,7-10* are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/22/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Sequnece Alignment #1*.



RD

## DETAILED ACTION

### *Election/Restrictions*

Applicant's election with traverse of Group I, claims 1, 2 and 7-10, in so far as they are drawn to a nucleic acid molecule associated with a metabolic disorder, in the reply filed on 2/22/2005 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 3-6 and 11-23 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

The restriction requirement mailed 11/22/2004 also included a further restriction if Group I was elected, to one of the sequences of SEQ NO: 1, 3, 5, 7, or 17. In Applicants' reply filed on 2/22/2005, the election of Group I did not include a further election as required.

During a telephone conversation with Kerri Pollard Schray on 4/6/2005 a provisional election was made with traverse to prosecute the invention of SEQ ID NO: 1. Affirmation of this election must be made by applicant in replying to this Office action.

Claims 1, 2 and 7-10, in so far as they are drawn to a nucleic acid of SEQ ID NO: 1, are under consideration.

### *Claim Objections*

Claims 1, 2 and 7-10 are objected to because the claims encompass non-elected inventions including polynucleotide sequences SEQ ID NO: 3, 5, 7 and 17, polypeptide sequences 2, 4, 6, 8 and 18, and methods of identifying a polypeptide associated with a metabolic disorder by contacting a sample with a compound that binds a polypeptide. Appropriate correction is required.

Claim 2 is also objected to because the claim encompasses two distinct methods with different method steps. Appropriate correction is required.

***Claim Rejections - 35 USC § 112, first paragraph, enablement***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2 and 7-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims are directed to a broad genus of methods. Claims 1 and 2 encompass a broad genus of methods of identifying a nucleic acid molecule associated with a metabolic disorder. Claims 7-10 encompass a broad genus of methods of identifying a subject having a metabolic disorder, or at risk of developing a metabolic disorder. The specification asserts that a nucleic acid molecule of SEQ ID NO: 1 is associated with a broad genus of metabolic disorders. This assertion is apparently based on the results found in Examples 3 and 4 (pages 80-82). These results show that genetically obese mice, genetically diabetic mice, and diet induced obese mice have

higher levels (6x, 3x, and 14.5x, respectively) of C3aR gene transcripts in white adipose tissue (WAT) than do wild type mice. However, the specification does not teach whether each result represents a single mouse or an average from several mice.

The relevant art teaches several genes wherein increased expression in white adipose tissue is correlated with obesity or diabetes in mice. For example, Xu teaches increased expression of several genes in WAT in genetically obese mice, diabetic mice, and diet induced obese mice versus wild type mice (Xu et al, 2003. Journal of Clinical Investigation. 112(12): 1821-1830). Furthermore, Xu teaches that 5 mice of each type were examined, and the results are presented with error bars showing the standard error. This standard is necessary for one of skill in the art to know that the difference presented in the results is significant. While it is possible that the data presented in the instant specification does represent an average of results measured in several mice, the specification does not teach the number of mice examined, or the ranges of individual data points measured and used to compute the average, or standard error based on statistical analysis of the data set. Therefore, the specification does not provide sufficient information such that one of skill in the art would believe that the results are significant. Without this information, one of skill in art would need to engage in undue experimentation to determine whether or not there actually is an increase in expression of the genes.

It is acknowledged that the level of skill of those in the art is high, but it is not disclosed and not predictable from the limited teachings of the prior art and specification whether or not the expression of the nucleic acid is correlated with any sort of metabolic disorder. Thus, the specification fails to teach the skilled artisan how to use SEQ ID NO: 1 in a diagnostic method without resorting to undue experimentation. The specification has not provided the person of ordinary skill in the art the guidance necessary to be able to use the polynucleotide for the above stated purpose.

Due to the large quantity of experimentation necessary to determine if the there is a correlation between SEQ ID NO: 1 and a metabolic disorder, the lack of direction/guidance presented in the specification regarding same, lack of working examples and the teachings of the prior art and the complex nature of the invention,

undue experimentation would be required of the skilled artisan to use the claimed invention. What Applicant has provided is a mere wish or plan and an invitation to experiment.

Even if a correlation was established between SEQ ID NO: 1 and obesity or diabetes in mice, claims 1, 2 and 7-10 would still rejected under 35 U.S.C. 112, first paragraph, because the specification, which would then be enabling for 1) a method of identifying a nucleic acid molecule associated with obesity or diabetic in mice in a sample by detecting SEQ ID NO: 1, or 2) a method of identifying a mouse that is obese or diabetic by detecting an increase in SEQ ID NO: 1 in white adipose tissue (WAT) by quantitative RT-PCR, does not reasonably provide enablement for 1) a method of identifying in a sample, a nucleic acid associated with a metabolic disorders, or 2) a method of identifying a subject having a metabolic disorder, or at risk for developing a metabolic disorder. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The breadth of claim 1, 2, and 7-10 is such that the claim methods encompass a genus of methods encompassing many species of methods that are not enabled. It would require an undue amount of experimentation to determine whether or not each of these methods would work as claimed. The embodiments that are not enabled are set forth as follows:

1) The claims encompass detection of <u>any</u> nucleic acid that binds to a compound that binds to SEQ ID NO: 1. The specification teaches RT-PCR using primers that bind to mRNA expressed by the gene of SEQ ID NO: 1. However, other compounds that bind to SEQ ID NO: 1 would also bind to other nucleic acids found in humans. For example, US Patent No. 6,555,339 teaches a nucleic acid sequence of a constitutively activated GPCR (SEQ ID NO: 245) that shares 21 nucleotides with instant SEQ ID NO: 1. See Sequence Alignment #1 that is attached to this Office Action. Therefore, a probe comprising these 21 amino acids would bind to SEQ ID NO: 1, but would also bind the GPCR taught by 6,555,339. Therefore, the method encompassed by the claims

encompasses detection of nucleic acids that may or may not be correlated with any metabolic disorder.

2) The claims encompass methods wherein SEQ ID NO: 1 is associated with any type of metabolic disorder. The specification teaches (page 7) that "the term "metabolic disorder" includes a disorder, disease or condition which is caused or characterized by an abnormal metabolism (i.e., the chemical changes in living cell by which energy is provided for vital processes and activities) in a subject". Even if the specification were to provide a correlation between expression of SEQ ID NO: 1 and obesity or diabetes in mice, it would not provide a correlation between expression of SEQ ID NO: 1 and any metabolic disorder other than obesity or diabetes.

3) Claims 7-10 encompass methods wherein a diagnosis of metabolic disorders is based on detection of SEQ ID NO: 1 in any sample from a subject. However, as Applicants themselves have shown, SEQ ID NO: 1 is present in wild type mice and is increased in expression in obese or diabetic mice. Therefore, a method directed just to detection of SEQ ID NO: 1 will not diagnosis obesity or diabetes. Only a detection of an *increase* in the amount of the mRNA expressed by a gene of SEQ ID NO: 1 as compared with wild type animals will lead to such a diagnosis. Furthermore, the sample that is taken from the individual must be from white adipose tissue (WAT). The specification does not teach the level of expression of SEQ ID NO: 1 in any other tissue in obese or diabetic mice, and therefore, measurements made with these tissues could not be used for diagnosis. Furthermore, these claims all encompass detection of genomic DNA of SEQ ID NO: 1. The specification has not taught any difference between the genomic DNA of non-obese and/or non-diabetic animals and the genomic DNA of obese and/or diabetic animals, and it is not predictable whether or not there is a difference, as gene expression (mRNA levels) can be increased without any change in the genomic DNA. Therefore, it is not predictable whether detection of genomic DNA of SEQ ID NO: 1 in a sample could be used to diagnosis obesity and/or diabetes in an animal.

4) Claims 7-10 encompass a method of diagnosis of a metabolic disorder in a subject of any species, including human. However, the specification only teaches

results as found in mice. While this result is certainly interesting and worthy of further study, it is not predictable whether the same expression will be seen in obese or diabetic humans, or other non-mouse animals.

5) Claims 7-10 encompass a method of identifying a subject at risk for developing a metabolic disorder. The specification has not demonstrated that this sort of risk assessment is possible for any species, even mice. Even if the specification were to establish an increase in SEQ ID NO: 1 expression in obese or diabetic mice, it would not provide a method of predicting whether or not a mouse is at risk of developing obesity or diabetes. The specification does not show if the increased expression causes the obesity or diabetes, or if the increase expression is as a result of these conditions. In order for one of skill in the art to practice the invention, a correlation between increased expression in non-obese and/or non-diabetic mice and the propensity to develop the disease would need to be established.

***Claim Rejections - 35 USC § 112, 1st paragraph, written description***

Claims 1-2 and 7-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. § 112, paragraph 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

In making a determination of whether the application complies with the written description requirement of 35 U.S.C. 112, first paragraph, it is necessary to understand what Applicants are claiming and what Applicants have possession of.

The claims are each drawn to a method comprising method steps that recite "a compound". The claims do not require that the compound to possess any particular conserved structure, or other distinguishing feature, other than that they bind to SEQ ID

NO: 1. The art recognizes that "compound" can pertain to chemical entities, pharmaceutical compositions, proteins, peptides, non-peptide compounds, animal tissue extracts, nucleic acids, antisense molecules, peptidomimetic, transformed cells, radiation, antibodies, antibody fragments, cyclic peptides, agonists, antagonists, inhibitors, enhancers, vegetable extracts, cell extracts, synthetic agents, biologically derived substances as well as proteinaceous substances, known, and unknown compounds. Therefore, each claim is drawn to a method using a genus of compounds.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only species of compound present in the claim that is sufficiently disclosed is a recitation of nucleic acids that bind SEQ ID NO: 1, e.g. probes and primers that bind to SEQ ID NO: 1. The specification does not identify any particular portion of the structure that must be conserved among the entire genus of compounds, nor does it provide a disclosure of structure/function correlation. The distinguishing characteristics of the claimed genus are not described. Accordingly, the specification does not provide adequate written description of the claimed genus. Therefore the full breadth of the claim fails to meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision.

### *Claim Rejections - 35 USC § 112, 2nd paragraph*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 2 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 is indefinite because it is unclear how the method steps lead to the identification required by the preamble. The preamble recites "a method of identifying a nucleic acid molecule ... associated with a metabolic disorder." It is unclear how detecting the presence of a nucleic acid molecule in a sample that binds to a compound that binds to SEQ ID NO: 1 would lead to the identification of a nucleic acid molecule associated with a metabolic disorder.

Claim 2 is indefinite because the relationship to claim 1, from which it depends, is unclear. Claim 2 recites, "The method of claim 1, wherein the detection of nucleic acid is a method selected from..." In claim 1, step (a) is "contacting a sample..." and step (b) is "detecting the presence of a nucleic acid..." Therefore, the preamble of claim 2 indicates that claim 2 limits part (b) of step 1. However, the steps presented in claim 2 present limitations that are drawn to both a "contacting a sample" step and a "detecting the presence of a nucleic acid" step. Therefore, it is unclear whether each of the steps of claim 2 are performed as part of step (b) of claim 1, or if the steps of claim 2 are meant to limit step (a) and (b) of claim 1. Clarity could be added to claim 2 by amending the preamble.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, and 7-10 and are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Ames et al. U.S. Patent No. 5,942,405, published 8/24/1999.

Claim 1 encompasses a method comprising the steps of (a) contacting a sample with a compound which binds to SEQ ID NO: 1; and (b) detecting the presence of SEQ

ID NO: 1 in the sample that binds to the compound, thereby identifying a nucleic acid molecule. The claim recites that the nucleic acid molecule must be "associated with a metabolic disorder". The instant application asserts that a molecule of SEQ ID NO: 1 is "associated with a metabolic disorder", therefore any method of detecting the presence of SEQ ID NO: 1 in a sample would inherently detect a molecule "associated with a metabolic disorder". Claim 2 encompasses a method of claim 1 wherein the nucleic acid is detected by (a) contacting the sample with two primers each comprising at least 25 contiguous nucleotides from SEQ ID NO: 1; (b) incubating the sample under conditions that allow nucleic acid amplifications; and (c) detecting the presence of a nucleic acid in the amplified sample.

Ames teaches a SEQ ID NO: 1 that is 100% identical to instant SEQ ID NO: 1. Ames further teaches (col 23, line 62 to col 27, line 6) polynucleotide assays using SEQ ID NO: 1. Ames further teaches (col 25, lines 1-7) "Polynucleotide primers may be used for amplifying C3a receptor cDNA isolated from a sample derived from a patient." Ames further teaches (col 25, lines 48-49) that primers are "comprised of at least 15 consecutive bases, and may contain at least 30 or even 50 consecutive bases." Therefore, Ames teaches a method that meets the limitations of instant claims 1 and 2.

Claim 7 encompasses a method comprising: (a) contacting a sample from a subject comprising nucleic acid molecules with compounds that bind to SEQ ID NO: 1; and (b) detecting the presence of a nucleic acid molecule in the sample. As the instant application teaches that SEQ ID NO: 1 is associated with a metabolic disorder, any method comprising these steps would inherently have all of characteristics of the claimed method. Claim 8 encompass a method of claim 7 wherein the nucleic acid is detected by (a) contacting the sample with two primers each comprising at least 25 contiguous nucleotides from SEQ ID NO: 1; (b) incubating the sample under conditions that allow nucleic acid amplifications; and (c) detecting the presence of a nucleic acid in the amplified. Claims 9 and 10 encompass a method of claim 7 wherein the method is used to detect mRNA (claim 9) or genomic DNA (claim 10) in the sample.

The method of Ames summarized above comprises a sample of a patient, and therefore meets all of the limitations of claim 7 and 8. Furthermore, the method of Ames

comprises using primers to amplify cDNA. The amplified cDNA is produced using primers that bind to mRNA (see col 25, line 40); therefore, the method of Ames detects mRNA and meets the further limitation of claim 9. Ames further teaches that genomic DNA can be directly detected (col 24, line 7), which meets the further limitation of claim 10.

In summary, the teachings of Ames clearly anticipate instant claims 1, 2 and 7-10.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 571-272-0829. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

zch

ROBERT S. LANDSMAN, PH.D.
PRIMARY EXAMINER

SEQUENCE ALIGNMENT #1

```
Qy       1441 ACTGTGTGA 1449
              |||||||||
Db       1441 ACTGTGTGA 1449


RESULT 4
US-09-826-509-36/c
; Sequence 36, Application US/09826509
; Patent No. 6806054
; GENERAL INFORMATION:
;  APPLICANT: Lehmann-Bruinsma, Karin
;  APPLICANT:  Liaw, Chen W.
;  APPLICANT:  Lin, I-Lin
;  TITLE OF INVENTION: No. 6806054-Endogenous, Constitutively Activated Known G
;  TITLE OF INVENTION:  Protein-Coupled Receptors
;  FILE REFERENCE: AREN-207
;  CURRENT APPLICATION NUMBER: US/09/826,509
;  CURRENT FILING DATE:  2001-04-05
;  PRIOR APPLICATION NUMBER: 60/195,747
;  PRIOR FILING DATE: 2000-04-07
;  PRIOR APPLICATION NUMBER: 09/170,496
;  PRIOR FILING DATE: 1998-10-13
;  NUMBER OF SEQ ID NOS: 589
;  SOFTWARE: PatentIn Version 2.1
; SEQ ID NO 36
;   LENGTH: 37
;   TYPE: DNA
;   ORGANISM: Homo sapiens
US-09-826-509-36

  Query Match             1.9%;  Score 28;  DB 4;  Length 37;
  Best Local Similarity   100.0%;  Pred. No. 0.00029;
  Matches   28;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy       1419 CATTTCAGAAAGAAATAGTACAACTGTG 1446
              ||||||||||||||||||||||||||||
Db         37 CATTTCAGAAAGAAATAGTACAACTGTG 10


RESULT 5
US-09-826-509-229
; Sequence 229, Application US/09826509
; Patent No. 6806054
; GENERAL INFORMATION:
;  APPLICANT: Lehmann-Bruinsma, Karin
;  APPLICANT:  Liaw, Chen W.
;  APPLICANT:  Lin, I-Lin
;  TITLE OF INVENTION: No. 6806054-Endogenous, Constitutively Activated Known G
;  TITLE OF INVENTION:  Protein-Coupled Receptors
;  FILE REFERENCE: AREN-207
;  CURRENT APPLICATION NUMBER: US/09/826,509
;  CURRENT FILING DATE:  2001-04-05
;  PRIOR APPLICATION NUMBER: 60/195,747
;  PRIOR FILING DATE: 2000-04-07
;  PRIOR APPLICATION NUMBER: 09/170,496
;  PRIOR FILING DATE: 1998-10-13
;  NUMBER OF SEQ ID NOS: 589
;  SOFTWARE: PatentIn Version 2.1
; SEQ ID NO 229
;   LENGTH: 40
;   TYPE: DNA
;   ORGANISM: Homo sapiens
US-09-826-509-229

  Query Match             1.5%;  Score 22;  DB 4;  Length 40;
  Best Local Similarity   100.0%;  Pred. No. 0.42;
  Matches   22;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy       1104 CGCCAAGTCTCAGAGCAAAACC 1125
              ||||||||||||||||||||||
Db          1 CGCCAAGTCTCAGAGCAAAACC 22


RESULT 6
US-09-826-509-230/c
; Sequence 230, Application US/09826509
; Patent No. 6806054
; GENERAL INFORMATION:
;  APPLICANT: Lehmann-Bruinsma, Karin
;  APPLICANT:  Liaw, Chen W.
;  APPLICANT:  Lin, I-Lin
;  TITLE OF INVENTION: No. 6806054-Endogenous, Constitutively Activated Known G
;  TITLE OF INVENTION:  Protein-Coupled Receptors
;  FILE REFERENCE: AREN-207
;  CURRENT APPLICATION NUMBER: US/09/826,509
;  CURRENT FILING DATE:  2001-04-05
;  PRIOR APPLICATION NUMBER: 60/195,747
;  PRIOR FILING DATE: 2000-04-07
;  PRIOR APPLICATION NUMBER: 09/170,496
;  PRIOR FILING DATE: 1998-10-13
;  NUMBER OF SEQ ID NOS: 589
;  SOFTWARE: PatentIn Version 2.1
; SEQ ID NO 230
;   LENGTH: 40
;   TYPE: DNA
;   ORGANISM: Homo sapiens
US-09-826-509-230

  Query Match             1.5%;  Score 22;  DB 4;  Length 40;
  Best Local Similarity   100.0%;  Pred. No. 0.42;
  Matches   22;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy       1104 CGCCAAGTCTCAGAGCAAAACC 1125
              ||||||||||||||||||||||
Db         40 CGCCAAGTCTCAGAGCAAAACC 19


RESULT 7
US-09-170-496D-245
; Sequence 245, Application US/09170496D
; Patent No. 6555339
; GENERAL INFORMATION:
;  APPLICANT: Behan, Dominic P.
;  APPLICANT:  Chalmers, Derek T.
;  APPLICANT:  Liaw, Chen W.
;  TITLE OF INVENTION: No. 6555339-Endogenous, Constitutively Activated Human G Protein-
;  TITLE OF INVENTION:  Receptors
;  FILE REFERENCE: AREN-0040
;  CURRENT APPLICATION NUMBER: US/09/170,496D
;  CURRENT FILING DATE:  1998-10-13
;  NUMBER OF SEQ ID NOS: 294
;  SOFTWARE: PatentIn version 3.1
; SEQ ID NO 245
;   LENGTH: 1071
;   TYPE: DNA
;   ORGANISM: Homo sapiens
US-09-170-496D-245

  Query Match             1.4%;  Score 21;  DB 4;  Length 1071;
  Best Local Similarity   100.0%;  Pred. No. 1.7;
  Matches   21;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy        118 GGCAATGGGCTGGTGCTGTGG 138
              |||||||||||||||||||||
Db        178 GGCAATGGGCTGGTGCTGTGG 198


RESULT 8
US-09-170-496D-269
; Sequence 269, Application US/09170496D
; Patent No. 6555339
; GENERAL INFORMATION:
;  APPLICANT: Behan, Dominic P.
;  APPLICANT:  Chalmers, Derek T.
;  APPLICANT:  Liaw, Chen W.
```

SEQUENCE ALIGNMENT #1

```
Qy       1441 ACTGTGTGA 1449
             |||||||||
Db       1441 ACTGTGTGA 1449


RESULT 4
US-09-826-509-36/c
; Sequence 36, Application US/09826509
; Patent No. 6806054
; GENERAL INFORMATION:
;  APPLICANT: Lehmann-Bruinsma, Karin
;  APPLICANT:  Liaw, Chen W.
;  APPLICANT:  Lin, I-Lin
;  TITLE OF INVENTION: No. 6806054-Endogenous, Constitutively Activated Known G
;  TITLE OF INVENTION:  Protein-Coupled Receptors
;  FILE REFERENCE: AREN-207
;  CURRENT APPLICATION NUMBER: US/09/826,509
;  CURRENT FILING DATE:  2001-04-05
;  PRIOR APPLICATION NUMBER: 60/195,747
;  PRIOR FILING DATE: 2000-04-07
;  PRIOR APPLICATION NUMBER: 09/170,496
;  PRIOR FILING DATE: 1998-10-13
;  NUMBER OF SEQ ID NOS: 589
;  SOFTWARE: PatentIn Version 2.1
; SEQ ID NO 36
;   LENGTH: 37
;   TYPE: DNA
;   ORGANISM: Homo sapiens
US-09-826-509-36

  Query Match             1.9%;  Score 28;  DB 4;  Length 37;
  Best Local Similarity   100.0%;  Pred. No. 0.00029;
  Matches   28;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy       1419 CATTTCAGAAAGAAATAGTACAACTGTG 1446
             ||||||||||||||||||||||||||||
Db         37 CATTTCAGAAAGAAATAGTACAACTGTG 10


RESULT 5
US-09-826-509-229
; Sequence 229, Application US/09826509
; Patent No. 6806054
; GENERAL INFORMATION:
;  APPLICANT: Lehmann-Bruinsma, Karin
;  APPLICANT:  Liaw, Chen W.
;  APPLICANT:  Lin, I-Lin
;  TITLE OF INVENTION: No. 6806054-Endogenous, Constitutively Activated Known G
;  TITLE OF INVENTION:  Protein-Coupled Receptors
;  FILE REFERENCE: AREN-207
;  CURRENT APPLICATION NUMBER: US/09/826,509
;  CURRENT FILING DATE:  2001-04-05
;  PRIOR APPLICATION NUMBER: 60/195,747
;  PRIOR FILING DATE: 2000-04-07
;  PRIOR APPLICATION NUMBER: 09/170,496
;  PRIOR FILING DATE: 1998-10-13
;  NUMBER OF SEQ ID NOS: 589
;  SOFTWARE: PatentIn Version 2.1
; SEQ ID NO 229
;   LENGTH: 40
;   TYPE: DNA
;   ORGANISM: Homo sapiens
US-09-826-509-229

  Query Match             1.5%;  Score 22;  DB 4;  Length 40;
  Best Local Similarity   100.0%;  Pred. No. 0.42;
  Matches   22;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy       1104 CGCCAAGTCTCAGAGCAAAACC 1125
             ||||||||||||||||||||||
Db          1 CGCCAAGTCTCAGAGCAAAACC 22


RESULT 6
US-09-826-509-230/c
; Sequence 230, Application US/09826509
; Patent No. 6806054
; GENERAL INFORMATION:
;  APPLICANT: Lehmann-Bruinsma, Karin
;  APPLICANT:  Liaw, Chen W.
;  APPLICANT:  Lin, I-Lin
;  TITLE OF INVENTION: No. 6806054-Endogenous, Constitutively Activated Known G
;  TITLE OF INVENTION:  Protein-Coupled Receptors
;  FILE REFERENCE: AREN-207
;  CURRENT APPLICATION NUMBER: US/09/826,509
;  CURRENT FILING DATE:  2001-04-05
;  PRIOR APPLICATION NUMBER: 60/195,747
;  PRIOR FILING DATE: 2000-04-07
;  PRIOR APPLICATION NUMBER: 09/170,496
;  PRIOR FILING DATE: 1998-10-13
;  NUMBER OF SEQ ID NOS: 589
;  SOFTWARE: PatentIn Version 2.1
; SEQ ID NO 230
;   LENGTH: 40
;   TYPE: DNA
;   ORGANISM: Homo sapiens
US-09-826-509-230

  Query Match             1.5%;  Score 22;  DB 4;  Length 40;
  Best Local Similarity   100.0%;  Pred. No. 0.42;
  Matches   22;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy       1104 CGCCAAGTCTCAGAGCAAAACC 1125
             ||||||||||||||||||||||
Db         40 CGCCAAGTCTCAGAGCAAAACC 19


RESULT 7
US-09-170-496D-245
; Sequence 245, Application US/09170496D
; Patent No. 6555339
; GENERAL INFORMATION:
;  APPLICANT: Behan, Dominic P.
;  APPLICANT:  Chalmers, Derek T.
;  APPLICANT:  Liaw, Chen W.
;  TITLE OF INVENTION: No. 6555339-Endogenous, Constitutively Activated Human G Protein-
;  TITLE OF INVENTION:  Receptors
;  FILE REFERENCE: AREN-0040
;  CURRENT APPLICATION NUMBER: US/09/170,496D
;  CURRENT FILING DATE:  1998-10-13
;  NUMBER OF SEQ ID NOS: 294
;  SOFTWARE: PatentIn version 3.1
; SEQ ID NO 245
;   LENGTH: 1071
;   TYPE: DNA
;   ORGANISM: Homo sapiens
US-09-170-496D-245

  Query Match             1.4%;  Score 21;  DB 4;  Length 1071;
  Best Local Similarity   100.0%;  Pred. No. 1.7;
  Matches   21;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy       118 GGCAATGGGCTGGTGCTGTGG 138
             |||||||||||||||||||||
Db       178 GGCAATGGGCTGGTGCTGTGG 198


RESULT 8
US-09-170-496D-269
; Sequence 269, Application US/09170496D
; Patent No. 6555339
; GENERAL INFORMATION:
;  APPLICANT: Behan, Dominic P.
;  APPLICANT:  Chalmers, Derek T.
;  APPLICANT:  Liaw, Chen W.
```